THE REMARKS

Claims 1, 2, 4-7, 9, 12-14, 18-21 and 23-27 are pending in the present application.

The specification is amended to insert the SEQ ID NOs.

Claims 1 and 4 are amended to recite "An antibody" instead of "A recombinant antibody product". Support for the amendment is found, for example, in page 2, line 15.

Claim 4 is amended to recite "cDNA" instead of "DNA". This amendment is to be clarify that the derivation of the DNA is from the cDNA of step a). Support for the amendment is found, for example, in Claim 4 as originally filed.

Claim 4 is amended to recite "introducing a mutation to the cDNA, wherein said mutation is the substitution of a cysteine with a polar amino acid at position H100A of the V_H domain according to the Kabat numbering system". This amendment is to clarify the introducing of a mutation to the cDNA as a separate step from the cloning step. Support for the amendment is found, for example, in Claim 4 as originally filed.

Support for new Claim 29 is found in Claim 2 as originally filed.

The above amendments are made solely in order to expedite prosecution of the application. Applicants reserve the right to file the original claims in one or more continuation-type application.

No new matter is added in any of the above amendment and the Examiner is respectfully requested to enter the amendments and reconsider the application.

The Response

1. Sequence Compliance

Applicants have amended the specification to identify the SEQ ID NOs. wherever sequences are cited in the specification. Therefore the present application fully satisfies the requirements of 37 CFR 1.821(d).

2. Objection Under 37 CFR 1.75(c)

The Examiner objects to claim 2 as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. As Claim 2 is cancelled,

Applicants respectfully request the Examiner withdraw this objection.

3. **Objection Under 37 CFR 1.75**

The Examiner objects to claim 18 as allegedly being a substantial duplicate of claim 9. As Claim 18 is cancelled, Applicants respectfully request the Examiner withdraw this objection.

4. **Rejection Under 35 U.S.C. 112, second paragraph**

(A) The Examiner rejects claims 4-7, 9, 12-14 and 18-21 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that there is insufficient antecedent basis for "the DNA" in steps b) to d) in Claim 4 and dependent Claims 5-7, 9, 12-14 and 18-21.

Amended Claim 4 recites "the cDNA" instead of "the DNA" in steps b) to e). Since term "the cDNA" has sufficient antecedent basis in Claim 4, Applicants respectfully request the Examiner withdraw this rejection.

(B) The Examiner rejects claims 4-6, 9, 12 and 18-20 as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner alleges that the omitted steps are: "the step that results in the serine found at position H100A of the product set forth in claims 1 and 2".

Claim 2 is cancelled, and Claim 4 is amended so that Claim 4 no longer depends from Claim 2. Claim 4 is amended to recite new step d): "introducing a mutation to the cDNA, wherein said mutation is the substitution of a cysteine with a polar amino acid at position H100A of the V_H domain according to the Kabat numbering system". New step d) describes a step which results in the substitution of the cysteine at position H100A of the V_H domain (according to the Kabat numbering system) with a polar amino acid.

Since amended Claim 4 recites a step that results in a polar amino acid at Position H100A, Applicants respectfully request the Examiner withdraw this rejection.

5. **Rejection Under 35 U.S.C. 112, first paragraph**

The Examiner rejects claims 1-2, 4-7, 9, 12-14, 18-21 and 27 as allegedly containing subject matter which was not described in the specification in such a way as to a reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

Amended Claims 1 and 4 recite "antibody" instead of "recombinant antibody product". Since the term "antibody" finds support in the specification in page 2, line 15, Applicants respectfully request the Examiner withdraw this rejection.

6. **35 U.S.C. § 103(a)**

The Examiner rejects Claims 1-2, 4-6, 9, 12, 18-20, 23-25 and 27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Kroon, et al. (*Pharmaceutical Res.* 9:1386-1393 1992) in view of Senoo, et al. (U.S. Patent No. 5,852,177) and Kipriyanov, et al. (*J. Immunol. Meth.* 196:51-62, 1996).

Kroon et al in fact teach away from the substitution of the cysteine at H100A of the V_H domain.

The Examiner alleges that "Kroon et al. provide clear motivation for producing an OKT3 antibody in which the Cys in CDR3 of the heavy chain was mutated in order to improve the stability of the therapeutic OKT3 antibody" (page 8, lines 15-17).

Regarding the cysteine at H100A of the V_H domain, Kroon, et al. disclose:

> "The most significant change in the peptide maps of OKT3 with long-term storage was a decrease in the size of the peak corresponding to H99-121 and the appearance of a new peak related to it by sequencing. This peptide does not contain Met; however, there is a non-sulfide-bonded Cys at residue 105, a likely candidate for oxidation. Due to the chemistry performed on this amino acid in preparing OKT3 for peptide mapping, the structural integrity of this Cys in the original sample could not be determined. Cys^{105} is part of the third CDR of the heavy chain, therefore, **degradative structural changes at this residue may have a significant impact on the binding affinity of the antibody**." (page 1390, left column, second paragraph; emphasis added).

Kroon, et al. teach away from the substitution of the cysteine at H100A of the V_H domain, when Kroon, et al. disclose that "**degradative structural changes at this residue may have a significant impact on the binding affinity of the antibody**". Since, based on

Kroon, et al., the cysteine at H100A of the V_H domain forms part of the complementarity-determining region ("CDR") of the OKT3 antibody, substituting this cysteine with another amino acid, including a polar amino acid or serine, may have a significant impact on the binding affinity of the antibody. The CDRs of an antibody participate in creating the binding site for the antigenic determinant. Consequently, changing the CDR of an antibody may negatively impact the binding affinity of such an antibody. Thus, based on Kroon, et al., one of ordinary skill in the art would be taught away from substituting the cysteine at H100A of the V_H domain because it may negatively impact the binding affinity of the OKT3 antibody. Such a mutated antibody, even if the stability was increased, could have a greatly reduced binding affinity that would render useless in binding antigen.

One seeking to increase the stability of the OKT3 antibody would also desire to retain the binding affinity of the OKT3 antibody. Consequently, Kroon, et al. teaches one away from substituting the cysteine at H100A of the V_H domain in order to increase the stability of the OKT3 antibody, because to do so would potentially negatively impact the binding affinity of the antibody. Therefore Kroon, et al. teach away from the substitution of the cysteine at H100A of the V_H domain.

There is no reasonable expectation of success that substituting the cysteine at H100A of the V_H domain of Kroon, et al. with the serine of Senoo, et al. would produce an antibody with almost no loss of its original binding affinity.

For the reasons provided earlier, since the cysteine at H100A of the V_H domain is part of a CDR of the OKT3 antibody, substituting it with another amino acid may result in a loss of binding activity. Therefore there is no reasonable expectation that, in substituting the cysteine at H100A of the V_H domain with a polar amino acid, or a serine, the antibody would still retain almost all of the binding affinity. There is no teaching in any of the cited references that suggests or motivates that making such a substitution would result in an antibody that retains almost all of the binding affinity. In fact, Kroon, et al., as stated earlier, teach the contrary.

In contrast, the present application teaches the claimed mutated antibodies are not decreased in binding activity as one skilled in the art might expect that "the mutated antibody has lost almost none of its original binding affinity even after one month of storage at 4°C in

PBS, whereas OKT3 has markedly lost binding affinity under these conditions (46%)." This loss of "almost none of its original binding affinity" is an unexpected result of the claimed substitution.

Relying on these cite references in order to arrive at the claimed antibody, and the method to produce the antibody, is based on the impermissible use of hindsight reasoning. There is no reasonable expectation that substituting the cysteine at H100A of the V_H domain of the OKT3 antibody with a polar amino acid, or a serine, would produce an antibody with an increased stability **and** with almost no loss of its original binding affinity.

Since the cited references do not render Claims 1-2, 4-6, 9, 12, 18-20, 23-25 and 27 obvious, Applicants respectfully request the Examiner withdraw this rejection.

The Examiner rejects Claim 26 under 35 U.S.C. §103(a) as allegedly being unpatentable over Kroon, et al. in view of Senoo et al. and Kipriyanov, et al., and in further view of Nitta, et al. (*The Lancet* 335:368-71, 1990).

The Examiner states that Nitta, et al. "teach a bispecific antibody comprising the anti-CD3 monoclonal antibody OKT3 and how to make it" (page 9, lines 21-22).

For the reasons provided earlier, Kroon, et al., Senoo, et al. and Kipriyanov, et al. do not render obvious an antibody comprising the V_H domain of the antibody produced by the hybridoma of ATCC deposit number CRL 8001, wherein the cysteine at position H100A of said V_H domain is substituted with a polar amino acid, or a method of producing the antibody.

The addition of Nitta, et al. does not overcome the defect of Kroon, et al., Senoo, et al. and Kipriyanov, et al.; as Nitta, et al. also do not teach that substituting the cysteine at the H100A position with a polar amino acid would result in an antibody with an increased stability **and** with almost no loss of its original binding affinity.

Since the cited references do not render Claim 26 obvious, Applicants respectfully request the Examiner withdraw this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe the application is in good and proper condition for allowance. Early notification of allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109. A telephone conference is especially requested if the Examiner intends to maintain the present rejections.

Respectfully submitted,

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